



## General

### Guideline Title

Chronic fatigue syndrome/myalgic encephalomyelitis. A primer for clinical practitioners.

### Bibliographic Source(s)

International Association for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (IACFS/ME). Chronic fatigue syndrome/myalgic encephalomyelitis. A primer for clinical practitioners. Chicago (IL): International Association for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (IACFS/ME); 2012. 41 p. [121 references]

### Guideline Status

This is the current release of the guideline.

## Recommendations

### Major Recommendations

#### Clinical Diagnosis

The diagnosis of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is based on the patient's history, pattern of symptoms, and the exclusion of other fatiguing illnesses. A symptom-based diagnosis can be made with published criteria. This primer uses the 2003 Canadian clinical case definition for ME/CFS (see worksheet in the original guideline document), because of its emphasis on clearly described core symptoms of the illness. The 1994 Fukuda criteria for CFS (Appendix A in the original guideline document) are primarily used for research purposes, although they may be required for disability determinations in the US and elsewhere. The newly published 2011 International Consensus Criteria for ME are not yet in general use. No specific diagnostic laboratory test is currently available for ME/CFS, although potential biomarkers are under investigation.

The diagnostic criteria for the 2003 case definition are listed in the clinical worksheet in the original guideline document and can be copied and used for patient diagnosis. The second page of the worksheet includes diseases which must be excluded or fully treated before a diagnosis of ME/CFS can be established. A number of non-exclusionary co-morbid entities which commonly co-exist with ME/CFS are also listed. Patients with ME/CFS may have many symptoms in addition to those listed in the case definition.

#### Patient History

A thorough medical and social history is essential for accurate diagnosis. Obtaining a succinct and coherent history within one visit may not be possible given the cognitive difficulties in some patients. The information gathered should include pre-illness functioning (education, job performance, social and family relationships) and current living circumstances (daily activities, stressors, major life changes, and support sources). Assessment of functioning will reveal the significant life changes experienced by the patient as a result of the illness. A review of previous medical records, reports, and lab tests supplied by the patient may also provide useful information.

Physical Examination

Physical findings are often subtle and may not be clearly evident. Patients may look pale and puffy with suborbital dark shadows or shiners. Examination of the patient's pharynx may show non-exudative pharyngitis (often referred to as "crimson crescents"). Cervical and axillary lymph nodes may be palpable and tender.

Some patients have demonstrable orthostatic intolerance with neurally mediated hypotension or postural orthostatic tachycardia syndrome, characterized by lowered blood pressure and/or a tachycardia on prolonged standing. This may be associated with dependent rubor in the feet and pallor of the hands.

A neurological examination may reveal a positive Romberg test or positive tandem stance test. If widespread pain is reported, a concurrent diagnosis of fibromyalgia should be considered and confirmed with a tender point examination.

Laboratory Tests

A basic laboratory investigation (Table 1, below) should be followed with more specific tests (Table 2, below) depending on particular symptoms. For example, an electrocardiogram (EKG/ECG) should be performed if chest pain is present, a chest x-ray obtained for cough, and testing for celiac disease if gastrointestinal symptoms are reported. (An endoscopy is recommended if symptoms are severe.)

Results of routine tests in patients with ME/CFS are usually within the normal range even during severe relapses. If abnormalities are found (e.g., elevated erythrocyte sedimentation rate [ESR]), other diagnoses may be considered.

Specific tests from Table 2 (below) may show low morning cortisol, elevated antinuclear antibody (ANA), and/or immunoglobulin abnormalities. In addition, vitamin D levels are often low, which would suggest bone density testing for osteoporosis. Any abnormal finding warrants further investigation to exclude other diseases.

Research studies have reported a number of immune, neuroendocrine and brain abnormalities in patients with ME/CFS, but the clinical value of expensive and elaborate tests for these abnormalities has not been established.

Table 1. Investigation of ME/CFS: Routine Laboratory Testing

<ul style="list-style-type: none"><li>• Full blood count and differential</li><li>• Erythrocyte sedimentation rate</li><li>• Electrolytes: sodium, potassium, chloride, bicarbonate</li><li>• Calcium</li><li>• Phosphate</li><li>• Fasting glucose</li><li>• C-reactive protein</li><li>• Liver function: bilirubin, alkaline phosphatase (ALP), gamma glutamyl transaminase (GGT), alanine transaminase (ALT), aspartate transaminase (AST), albumin/globulin ratio</li><li>• Renal function: urea, creatinine, glomerular filtration rate (eGFR)</li><li>• Thyroid function: thyroid stimulating hormone (TSH), free thyroxine (free T4)</li><li>• Iron studies: serum iron, iron-binding capacity, ferritin</li><li>• Vitamin B12 and serum folate</li><li>• Creatine kinase (CK)</li><li>• 25-hydroxy-cholecalciferol (vitamin D)</li><li>• Urinalysis</li></ul>
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Table 2. Investigation of ME/CFS: Tests to Be Considered Depending on Symptoms

<ul style="list-style-type: none"><li>• Antinuclear antibodies</li><li>• Chest x-ray</li><li>• Electrocardiogram (EKG/ECG)</li><li>• Endoscopy: gastroscopy, colonoscopy, cystoscopy</li><li>• Estradiol and follicle-stimulating hormone</li><li>• Gastric emptying study</li><li>• Gliadin and endomysial antibodies</li><li>• Immunoglobulins</li><li>• Infectious disease screen if human immunodeficiency virus (HIV), hepatitis, Lyme disease, Q fever, etc. are possible</li><li>• Microbiology: stools, throat, urine, sputum, genital</li></ul>
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- Morning cortisol
- Magnetic resonance imaging (MRI) if multiple sclerosis suspected
- Overnight polysomnogram and possibly multiple sleep latency test
- Prolactin
- Renin/aldosterone ratio
- Rheumatoid factors
- Serum amylase
- Short adrenocorticotrophic hormone (ACTH) challenge test or Cortrosyn stimulation test
- Testosterone
- Tilt table test for autonomic function

## Differential Diagnosis

Although the symptoms of a number of diseases can mimic ME/CFS, the presence of post-exertional symptom exacerbation, a key feature of the illness, increases the likelihood of ME/CFS as the correct diagnosis. Table 3 in the original guideline document lists a number of medical conditions that need to be considered in the differential diagnosis.

### Distinguishing ME/CFS from Depressive and Anxiety Disorders

Symptoms of depression or anxiety may result from or precede the illness as they do with other chronic medical conditions. Distinguishing depressive and anxiety disorders from ME/CFS may present a challenge. Depressive symptoms, including problems with sleep, cognition, and initiating activity as well as fatigue and appetite/weight changes may overlap with ME/CFS.

Differential diagnosis is based on the identification of ME/CFS features—in particular, post-exertional malaise (PEM)—as well as autonomic, endocrine or immune symptoms (see Diagnostic Worksheet in the original guideline document). PEM is the exacerbation of symptoms following minimal physical or mental activity that can persist for hours, days or even weeks. For instance, a short walk may trigger a long-lasting symptom flare-up. By contrast, patients with major depression generally feel better after increased activity, exercise or focused mental effort.

Furthermore, patients with ME/CFS (with or without co-morbid depression) generally have strong desires to be more active, but are unable to do so. In clinical depression, by comparison, there is often a pervasive loss of interest, motivation and/or enjoyment. Finally, diurnal fluctuations in ME/CFS tend to show symptom-worsening in the afternoon while in major depressive disorder more severe symptoms often occur in the morning.

Some patients with ME/CFS do develop major depressive disorder which is characterized by low mood (loss of interest is less likely) and additional symptoms such as feelings of worthlessness or guilt and suicidal ideation. The practitioner should conduct a suicide evaluation for all patients who appear to be clinically depressed or highly stressed.

Secondary anxiety can arise with the crisis of illness onset and persist as the illness affects the ability to work and family relationships. Secondary anxiety may be distinguished from generalized anxiety disorder (GAD). GAD is characterized by excessive worry and assorted physical symptoms. By comparison, panic disorder features unbidden panic attacks. Symptoms of ME/CFS not found in GAD and panic disorders include post-exertional malaise as well as autonomic, endocrine or immune symptoms (see Diagnostic Worksheet in the original guideline document). In addition, patients with primary anxiety disorders generally feel better after exercise whereas exercise worsens symptoms in ME/CFS. Finally panic disorder is situational and each episode is short-lived, whereas ME/CFS persists for years.

### Exclusionary Medical Conditions (Table 3 in the original guideline document)

ME/CFS is not diagnosed if the patient has an identifiable medical or psychiatric condition that could plausibly account for the presenting symptoms. However, if ME/CFS symptoms persist after adequate treatment of the exclusionary illness, then a diagnosis of ME/CFS can subsequently be made.

### Co-existing Medical Conditions (Table 4 in the original guideline document)

A number of other (non-exclusionary) conditions may co-exist with ME/CFS. A listing of these conditions appears in Table 4 in the original guideline document and includes fibromyalgia, multiple chemical sensitivity, irritable bowel syndrome, irritable bladder syndrome, interstitial cystitis, temporomandibular joint syndrome, migraine headache, allergies, thyroiditis, Sicca syndrome, Raynaud's phenomenon, and prolapsed mitral valve. These conditions should be investigated in their own right and treated appropriately.

## Management/Treatment

The onset of ME/CFS impacts the individual's ability to work, to sustain family and social relationships, to provide basic self-care, and to maintain self-identity. These sudden losses may trigger confusion and crisis. Yet patients often receive little benefit from consultations with health

practitioners due to (1) physician skepticism of individuals with ME/CFS who may not look ill and show normal findings on standard physical examinations and laboratory tests; and (2) the absence of a clear standard of care for these patients. These obstacles, in addition to significant illness limitations and unsupportive family and friends, may lead to patients feeling demoralized, frustrated and angry.

This section provides recommendations primarily for ambulatory patients who are able to attend office visits. Special considerations are offered in the "Related Clinical Concerns" section for the perhaps 25% of patients with ME/CFS who are bedridden, house-bound, or wheelchair dependent.

### Approach to Treatment

Given the absence of curative treatments, clinical care of ME/CFS involves treating symptoms and guiding patient self-management. The goal is symptom reduction and quality of life improvement based on a collaborative therapeutic relationship. Although not all patients will improve, the potential for improvement, which ranges from modest to substantial, should be clearly communicated to the patient.

Acknowledging that the patient's illness is real will facilitate a therapeutic alliance and the development of an effective management plan. Thus, patients may be greatly relieved to hear that their bewildering symptoms have a diagnostic label—an important validation of their concerns. The practitioner can also assure the patient that normal findings on diagnostic tests do not negate the reality of the illness.

Once the diagnosis is established, a systems review will reveal the patient's most troublesome symptoms and concerns. These may include several of the following: debilitating fatigue and activity limitations; sleep disturbance; pain; cognitive problems; emotional distress; orthostatic intolerance; gastro-intestinal or urological symptoms; gynecological problems.

The clinical management plan in this section focuses on both non-pharmacologic interventions and medications. Written educational material for patients can also be helpful because they may have short-term memory problems.

To improve clinical management, the following are suggested:

- A patient support person to take down medical advice or a recording of the visit for later patient review
- Obtaining a written list of the patient's most troublesome symptoms
- Agreement with the patient to focus on a limited number of selected symptom(s) in order to avoid overloading the patient
- Medication doses that start low and go slow
- Ongoing assessments of the patient over multiple visits

The order of ME/CFS symptoms presented below starts with those considered most treatable.

### Sleep

The non-restorative sleep in ME/CFS indicates waking up feeling unrefreshed or feeling as tired as the night before. The unrefreshed feeling may be associated with morning stiffness or soreness and mental foggy that may last for an hour or two. Disturbed sleep patterns include difficulty falling or staying asleep, frequent awakenings, or coma-like sleep. Hypersomnia may occur in the early stages of the illness. Many patients have a diagnosable sleep disorder that may require consultation with a sleep disorder specialist.

The following sleep hygiene suggestions may be helpful to patients:

- An hour of relaxing wind-down activities prior to bed time
- Regular sleep and wake times
- Pacing activities during the day to avoid symptom exacerbation that may interfere with sleep
- Avoiding naps after 3 pm and substituting rest
- Spending some morning time under full spectrum light either outdoors, by a window, or artificial light
- Reducing or eliminating caffeine-containing beverages and food
- Using earplugs or soundproofing for noise, or sleeping in a different bedroom without (a snoring) partner
- Ensuring the bedroom is very dark by using a sleep mask or black-out curtains
- If unable to sleep, getting up and moving to another room, and doing a quiet activity (reading, soft music, or relaxation tapes; not a computer, iPad, or TV) until sleepy
- Using the bed for sleeping and sex only
- Avoiding attempts to force sleep

### *Medications (Table 5 in the original guideline document)*

All sedating medications must be safe for long-term use and should be started at a low dose. The medication should be taken early enough so that

sedation takes effect around bed time. Patients may initially feel thick-headed in the morning, but this usually improves as benefits become apparent. The risk of side effects and drug combinations which can produce serotonin syndrome should be explained. In some patients, tolerance may develop with medications. Rotating medications may be more effective than using a single drug.

## Pain

Persistent pain in ME/CFS, whether widespread or localized, may range from mild to severe. In some cases the patient may feel pain from minimal stimulation such as a gentle touch. Headaches may be particularly troublesome and are often migrainous. If chronic widespread pain is a major complaint, a fibromyalgia evaluation may be indicated.

Helpful non-pharmacologic interventions for pain may include pacing of activity, physical therapy, stretches, massage, acupuncture, hydrotherapy, chiropractic, yoga, Tai Chi and meditation (relaxation response). Also consider hot or cold packs, warm baths or balneotherapy, muscle liniments, electrical massagers, TENS (transcutaneous electrical nerve stimulation), and rTMS (transcranial magnetic stimulation). These methods can be effective singly or in various combinations to reduce tension and pain. However, these interventions may also be poorly tolerated, inaccessible, or prohibitively costly. It is important to treat localized pain, e.g., arthritis or migraine, because it can amplify the generalized pain of ME/CFS.

### *Medications (Table 6 in the original guideline document)*

For the treatment of pain in ME/CFS, the lowest effective dose should be prescribed and increased cautiously. Patients with severe pain may need the stronger analgesics and narcotics. Although opiates should be discouraged for the treatment of chronic pain states, they may be beneficial in some cases. Their use requires a clear rationale with documentation. Providers should consider referring such patients to a pain specialist.

## Fatigue and Post-exertional Malaise

Patients with ME/CFS experience abnormal fatigue that is both more intense and qualitatively different from normal tiredness. The fatigue in ME/CFS may take several different forms: post-exertional fatigue (abnormal exhaustion or muscle weakness following minor physical activity), persistent flu-like feelings, brain fog (mental exhaustion from everyday cognitive effort), and wired fatigue (feeling over-stimulated when very tired).

The type of fatigue that is a core feature of ME/CFS is post-exertional malaise (PEM). PEM is the exacerbation of fatigue and other symptoms (e.g., cognitive difficulties, sore throat, insomnia) following minimal physical or mental activity that can persist for hours, days or even weeks. PEM may be related to abnormal energy metabolism.

Energy for physical activities is produced through two physiological systems: (1) Anaerobic metabolism is the predominant metabolic pathway during the first 90 seconds of exercise; (2) the aerobic/oxidative system is the primary source of energy during physical activities lasting longer than 90 seconds.

Because most daily physical activities exceed 90 seconds, the aerobic system is typically utilized to produce the energy-releasing nucleotide, adenosine triphosphate (ATP) at a steady rate in order to perform activities of daily living. In patients with ME/CFS, aerobic metabolism may be impaired. Thus, any physical exertion exceeding 90 seconds may utilize a dysfunctional aerobic system, which leads to increased reliance on anaerobic metabolism. This imbalance may be linked to the prolonged symptoms and functional deficits associated with PEM.

Simple and inexpensive physiological measures, such as heart rate monitoring, may be used to ensure that real-time cardiovascular responses remain below the threshold of aerobic impairment.

### *Managing Post-exertional Symptoms: Pacing and the Energy Envelope*

Fatigue improvement can be facilitated by advising patients to pace or "spread out" activities so that ongoing exertion remains below the threshold of post-exertional symptom flare-ups (see Figure 2 in the original guideline document). For instance, rather than completing housework in one uninterrupted push, tasks may be divided into smaller pieces with rest intervals interspersed. Remaining as active as possible while avoiding fatigue-worsening over-exertion delineates an optimal zone of activity termed the "energy envelope." An activity log (Appendix D in the original guideline document) may be helpful to identify personal activities that stay within or exceed that optimal range.

### *Activity and Exercise*

To stay within the energy envelope, some patients need to decrease their activity while others need to carefully and selectively do more. Many individuals with ME/CFS mistakenly over-exercise in an attempt to reduce fatigue and other symptoms. In addition, well-meaning healthcare providers may recommend exercise for patients with ME/CFS using guidelines intended for healthy people. Such guidelines are generally inappropriate and often counterproductive in this illness. Thus, practitioners may push patients too hard and patients may push themselves into activities that worsen symptoms. This symptom-worsening may be linked to underlying aerobic impairment.

Misdirected exercise usually results in post-exertional symptom flare-ups or relapses which discourage further exercise. In contrast, the optimal amount of individualized exercise is usually well below standard recommendations for healthy individuals, avoids post-exertional symptoms, and promotes improvement.

### *Exercise Recommendations*

An individualized activity plan should be developed in collaboration with the patient. Consultation with rehabilitation professionals knowledgeable about ME/CFS may also be desirable. Any exercise or activity program should seek to minimize the negative effects of exertion on impaired aerobic function. Exercise should also not take priority over activities of daily living.

Initially, the patient's degree of activity limitation can be estimated using a functional status rating such as the Functional Capacity Scale (Appendix C in the original guideline document). This 10 point scale ranges from 10, for symptom free individuals, to 1, for patients who are bedridden and unable to perform activities of daily living.

### Severely Ill Patients (Functional Capacity Rating 1-3; Appendix C in the original guideline document)

Homebound and bedbound patients may benefit from in-home services that provide assisted range-of-motion and strengthening exercises. Exercise lying down should be advised when exercise standing or sitting is poorly tolerated. Initially, interval training exercise should begin with gentle stretching to improve mobility utilizing intervals of 90 seconds or less. The patient should rest between intervals until complete recovery has occurred. Additional intervals can be added when the stretching exercises do not trigger post-exertional symptoms. Then, resistance training can begin (functional capacity rating 4-5) with elastic bands or light weights. As endurance improves, short-duration interval training such as leisurely-paced walking can be added.

### Higher Functioning Patients (Functional Capacity Rating 5-9; Appendix C in the original guideline document)

Interval training can begin with leisurely paced walking, swimming, or pedaling on an exercise cycle. The initial duration may vary from 5-15 minutes a day depending on how much the patient can do without provoking symptom flares. These higher functioning patients may also benefit from adaptive yoga and Tai Chi.

### *Medications for Fatigue and Post-exertional Symptoms (Table 7 in the original guideline document)*

Due to prescribing difficulties, cost, and limited effectiveness, medications for fatigue may need to be reserved for functional assistance at special, but potentially exhausting events in the patient's life (e.g., a wedding or a concert). If the medication is effective, patients should avoid exceeding their individual activity limit, as this is likely to provoke symptom-worsening. Thus, careful monitoring of activity is recommended.

### *Cognitive Problems*

The patient's cognitive difficulties can be managed to some extent with the following suggestions:

- Using a "memory book" to write things down in one place (and attempt not to lose the book)
- Developing habits such as leaving keys or glasses or always parking in the same spot
- When possible, avoiding situations involving multisensory bombardment and fast-paced activity
- Limiting the duration and intensity of cognitive efforts (a form of pacing)
- Limiting or stopping cognitive efforts when cognitive symptoms flare up

### *Medications for Cognitive Problems (Table 8 in the original guideline document)*

Stimulants seem to work best when the patient describes excessive "sleepiness" during the day as opposed to "tiredness." Sleepiness is suggested by a score of >10 on the Epworth sleepiness scale which may warrant a workup for primary sleep disorders.

### *Depression, Anxiety and Distress*

The prevalence of clinical depression and/or anxiety in patients with ME/CFS is about 40%. This is similar to the rates of psychiatric symptoms in other chronic conditions such as arthritis. Patients may develop depression, anxiety, or stress reactions secondary to the illness or evidence a history of depression/anxiety prior to illness onset. The practitioner should conduct a suicide evaluation for all patients who appear to be clinically depressed or highly stressed.

### *Managing Depression, Anxiety and Distress: Support, Coping Skills and Pleasant Experiences*

These types of interventions may be helpful:

- Educating family members about the illness so that they can provide useful assistance and support
- Identifying and scheduling pleasurable low effort activities (music, recorded relaxation, observing nature) which can generate well-being, reduce symptoms of anxiety, depression and distress and lessen fatigue as well
- Developing coping skills, such as cognitive strategies to reduce anger, worry, and catastrophizing, as well as skills to improve tolerance of this difficult illness. Good resources are available to guide ME/CFS patients with effective coping skills
- Referral, if needed, to supportive counseling, preferably to a professional familiar with ME/CFS
- Referral to a ME/CFS support group or volunteer services. Successful support groups have effective leadership and positive programming that avoids simply exchanging complaints

### *Medications for Depression*

For patients who are clinically depressed, medication can sometimes improve mood and reduce fatigue. Medications should be started at a low dose. Improvement may take several weeks. Possible side effects of antidepressants, notably sedation and orthostatic hypotension, may worsen fatigue and autonomic lability in some patients. Drug choice is often based on side effects profile and the patient's response.

### *Cognitive Behavioral Therapy (CBT)*

CBT is a much publicized and debated psychotherapeutic intervention for ME/CFS that addresses the interactions between thinking, feeling and behavior. It focuses on current problems and follows a structured style of intervention that usually includes a graded activity program. CBT may improve coping strategies and/or assist in rehabilitation, but the premise that cognitive therapy (e.g., changing "illness beliefs") and graded activity can "reverse" or cure the illness is not supported by post-intervention outcome data.

In routine medical practice, CBT has not yielded clinically significant outcomes for patients with ME/CFS. Furthermore, the lack of CBT providers who specialize in this illness (psychologist, social worker, or nurse) indicates that CBT may not be an option for many patients with ME/CFS. More detailed information on CBT protocols and the controversy surrounding its application in ME/CFS is presented elsewhere.

### *Management of Related Conditions*

See section 5:8 of the original guideline for information on managing the following related conditions:

- Orthostatic intolerance (OI) and cardiovascular symptoms
- Gastrointestinal problems
- Urinary problems
- Allergies
- Multiple chemical sensitivity (MCS)
- Infections and immunological factors

### *Dietary Management*

Although no evidence-based special diet is available for ME/CFS, dietary programs are popular with many patients. Good nutrition with a sensible, balanced diet is advisable. Excesses of specific foods as well as rich, fatty foods, sugars and caffeine are best avoided. Eating small meals with snacking in between can be helpful. To help counteract the risk of osteoporosis from lack of vitamin D, dairy products should be incorporated in the diet if lactose intolerance or an allergic reaction to milk and milk products is not present. In addition, because alcohol intolerance (causing sedation) may be reported, alcohol use should be minimized or avoided.

Some individuals who attribute their ME/CFS to food intolerances will carefully avoid certain foods. Gluten and/or lactose intolerances, not uncommon in ME/CFS, require a gluten- or lactose-free diet. Provided that these intolerances have been excluded, a rotational approach, rather than absolute avoidance, may lessen possible negative reactions to food.

Although there is no evidence that patients with ME/CFS suffer from systemic candidiasis, diets intended to combat candidiasis and allergies are quite popular and many patients believe that they are helpful. Finally, some patients with gastrointestinal symptoms have reported benefit from a "leaky gut diet" in combination with L-glutamine or butyrate.

### *Dietary Supplements*

Patients with ME/CFS need to ensure that they obtain at least the recommended daily allowance (RDA) of vitamins and minerals. This is not always possible using dietary sources. A suitable multivitamin and a separate multi-mineral preparation will ensure that at least the RDA of vitamins and minerals are obtained in the correct proportions.

### Vitamin D

Because vitamin D deficiency is often found in ME/CFS, additional vitamin D may be necessary to achieve an optimal level, which may reduce the risk of osteoporosis, cancer, heart disease, stroke, and other illnesses.

### Vitamin B12 and B-Complex

Given that cerebrospinal fluid levels of vitamin B12 may be depleted in some patients with ME/CFS, a trial of a weekly injection of hydroxycobalamin 1000 µg for six weeks (or perhaps longer) may be helpful. There are no reports of serious risk or side effects, despite the high blood levels achieved. A supplement of B-complex will avoid concurrent B vitamin deficiency.

### Essential Fatty Acids

Essential fatty acids supplementation in ME/CFS has yielded symptom improvement and greater shifts towards normal levels of cell fatty acids concentration in treated patients in some studies. Eicosapentaenoic acid, an essential fatty acid, is a major component of omega-3 fish oil. This substance has been beneficial in reducing symptoms for some patients. Additional vitamin and mineral cofactors, including biotin, niacin, folic acid, vitamin B6, vitamin B12, vitamin C, selenium, zinc, and magnesium, may be supportive in conjunction with essential fatty acids supplementation.

### Zinc

Inadequate zinc intake may contribute to decreased function of natural killer cells and cell-mediated immune dysfunction. A multi-mineral preparation may ensure the correct balance between zinc and copper.

### Herbs

Patient use of herbal/natural remedies should be identified to reveal likely side effects and avoid potential conflicts with prescribed medications. Patients may not know that "natural" does not necessarily mean "better" or "safe." As with medication, small doses should be used initially with warnings about adverse reactions. Some herbs with pharmacological effects have been traditionally incorporated in the diet, e.g., herbal teas of peppermint, ginger or chamomile for gastrointestinal symptoms or for improving sleep.

Warnings are appropriate for several largely unregulated products. Glyco-nutrients, olive leaf and pycnogenol (pine bark) have been touted as potential cures for ME/CFS, but neither clinical observation nor published evidence supports their use. Products claiming to be immune system boosters have not been shown, in the medical literature, to reduce symptoms in ME/CFS patients. Many of the so-called adrenal support concoctions contain steroids, which can have adverse effects in those who do not need them, especially when stopped suddenly. Steroids should only be prescribed by a physician.

### Alternative and Complementary Approaches

Patients with ME/CFS often try costly alternative treatments in search of a cure. A review of a number of studies revealed generally poor methodologies and little evidence for more than modest effects. Equivocal evidence was found for homeopathy and biofeedback. Acupuncture, massage and chiropractic are relatively established treatments for pain, and thus are covered in the pain section. More detailed information may be found in recent reviews.

### Follow Up

Patients with ME/CFS require regular reassessment and follow-up to manage their most disabling symptoms and to reconfirm or change the diagnosis. Although patients may assume that new symptoms are part of ME/CFS, other illnesses with symptoms not characteristic of ME/CFS can develop and should be investigated. Any patient who experiences a worsening of symptoms or the onset of new and/or additional symptoms should be encouraged to return to the physician's office. Additionally, an annual follow-up should be undertaken that includes a review of symptoms, a physical exam, a functional capacity evaluation, routine screening (Table 1, above), and a review of the patient's management/treatment plan.

### Related Clinical Concerns

#### Low Functioning Patients: Special Considerations

Perhaps one in four patients are so disabled that they are confined to a bed or chair and rarely leave home. These individuals are unable to attend regular office visits. Assessments also reveal greater symptom severity, more comorbidities, limited mental activity, and very low levels of physical activity. A small minority of these patients may be totally bedbound and report constant pain as well as an inability to tolerate movement, light or noise and certain scents or chemicals (including prescribed drugs).

Home-based caregivers are essential to support patients with severe ME/CFS, and to participate in their ongoing management plan. Caregivers can also be subject to considerable stress in serving the needs of the patient.



These suggestions may be helpful for this severely ill group:

- Recommend a very quiet environment.
- Limit mental activity (such as reading, writing, computing, or concentrating) because mental exertion is as exhausting as physical activity in many of these patients.
- Minimize medications and supplements to those absolutely necessary.
- Prescribe medication in very low doses and titrate slowly, as tolerated.
- Proceed very slowly with any activity, perhaps starting with range of motion exercises lying down, followed by range of motion with light resistance and then very light aerobic activity.

In addition, low functioning patients may require more services and support with respect to:

- Follow up (perhaps via home visits, telephone contacts, or online communication)
- Social support, including home health services and aides
- Stress management and grief/loss counseling
- Modest expectations for themselves and from others
- Balanced nutrition and healthy foods (provided and prepared by caretakers)

### Pregnancy

Most mothers with ME/CFS have an uneventful pregnancy and deliver a normal child. During pregnancy, ME/CFS symptoms may improve for some, remain the same for some, and worsen for others. In many patients, symptoms return to pre-pregnancy levels within weeks of delivery. Pregnancy is not recommended in the early stages of ME/CFS, because the patient may be very ill and the diagnosis uncertain.

Some medications for ME/CFS can damage a growing fetus especially in the early stages of pregnancy. The effects of most herbal preparations on the fetus are unknown. Healthcare providers should advise which ongoing medications, given their risks to the fetus, should be stopped before a planned pregnancy. The patient can then determine if she can cope with possibly worsened ME/CFS symptoms without the medications. Some essential medications may need to be continued in smaller doses.

Obstetric problems, which may be more prevalent in women with ME/CFS, include lowered fertility, miscarriage, severe vomiting in pregnancy, exhaustion in labor, delayed post-partum recovery and post-partum depression. If labor is prolonged, surgical delivery of the child is recommended.

Lactation is not contraindicated. The advantages and disadvantages of breast-feeding should be discussed with the mother. Milk can be expressed for night feedings, to allow the mother adequate rest. Child-rearing is the biggest challenge for mothers with ME/CFS and many require a good support network.

The offspring of mothers with ME/CFS may have a higher risk of developing ME/CFS than the general population. One study showed a 5% risk of developing ME/CFS in childhood or early adult life. Another small study suggests that the offspring also may have an increased risk of developmental delays and learning difficulties.

### Gynecological Problems

ME/CFS and some common gynecological conditions such as pre-menstrual syndrome and menopause show a significant overlap of symptoms. These conditions also frequently exacerbate symptoms of ME/CFS and vice versa.

A small number of scientific studies suggest that several gynecological conditions occur more frequently in women with ME/CFS. Some of these conditions may pre-date the onset of the illness. These disorders include: premenstrual syndrome; anovulatory and oligo-ovulatory cycles; low estrogen levels leading to a multitude of central nervous system (CNS) symptoms, loss of libido, and in later years, osteoporosis; dysmenorrhea; pelvic pain; endometriosis; interstitial cystitis; dyspareunia and vulvodynia; and a history of hysterectomy (for fibroids or ovarian cysts). The investigation and treatment of these conditions should follow standard gynecological practice.

Many peri-menopausal and postmenopausal patients with ME/CFS may benefit from hormone replacement therapy (HRT). Pre-menopausal patients with ME/CFS and low estrogen levels may also be helped by HRT. Estrogen may improve cerebral circulation, benefit cognition, and provide significant relief from hot flashes, insomnia, and fatigue. HRT also reduces the risk of osteoporosis.

Some women may be more responsive to a progesterone-only regimen such as a progesterone-only pill, or impregnated intra-uterine device. These approaches also address contraception, which may be vital for women with ME/CFS. Oral contraceptives may help patients who suffer

from menstrual pain, particularly if bleeding is heavy.

Hormonal therapy should be limited in duration due to the increased risk of breast, ovarian and uterine cancer with HRT. Some women prefer to take "natural" hormones (e.g., phytoestrogens and wild yam products), but it should be pointed out that prospective randomized studies of their clinical effects and potential side effects have not been done.

### Pediatric ME/CFS

ME/CFS can occur at any age but it is difficult to diagnose under the age of ten. Pediatric management can be especially challenging. Children and adolescents sometimes do not report symptoms and assume tiredness is normal. In addition, they are often misdiagnosed as lazy or having behavioral disorders, school phobia, attention deficit hyperactivity disorder (ADHD) or factitious disorder by proxy. The diagnosis of ME/CFS is often overlooked or delayed, but it can be established using a specific pediatric case definition (Appendix B in the original guideline document), which is based on the Canadian case definition. The diagnosis in children can be made after 3 months of illness. The prevalence of ME/CFS in children and adolescents varies greatly in different studies, but, overall, rates appear to be lower than in adults.

Management and treatment of children with ME/CFS is similar to that described above for adults. Any medications should be prescribed with great caution. As with adults, many pediatric patients with ME/CFS respond to much lower than standard doses of medications.

Many children with ME/CFS experience worsening of their school performance. In the USA, children and adolescents with cognitive deficits and physical limitations may qualify for special services under the Individuals with Disabilities Education Act (IDEA), because they are "health impaired." With physician documentation, eligible students can receive an individualized educational plan (IEP).

Tutoring at home, correspondence schooling or home schooling allows students who are debilitated with ME/CFS to pace themselves and reduce symptom flares. When appropriate, a graduated schedule of return to school can be successful in conjunction with school personnel who are willing to work with the child and family. This might involve the child initially attending a single class on a daily basis and gradually increasing the number of classes attended over several weeks or months.

To enhance the chances of recovery, competitive sports are best avoided. If the patient is subject to stress-related symptom flare-ups, it may be desirable to limit academic examinations to those that are deemed essential. Family counseling may be recommended if family conflicts related to the child's illness are evident. The prognosis for children with ME/CFS is considerably better than for adults, although they may initially be severely ill.

### Immunizations

Patients with ME/CFS should consider avoiding all but essential immunizations particularly with live vaccines, as post-vaccination relapse has been known to occur. Usual medical practice is not to vaccinate a normally healthy person when unwell. However, during a flu epidemic, patients should balance the health hazards of becoming ill against the possibility of symptom-worsening due to immunization.

### Blood and Tissue Donation

The American Red Cross requires that blood donors "be healthy," i.e., feel well and be able to perform normal activities. Since people with ME/CFS are not healthy by this definition, they should not donate blood. Furthermore, based on the possible link between ME/CFS and xenotropic murine leukemia virus-related virus (XMRV), a number of national blood banks adopted measures to discourage or prohibit individuals diagnosed with ME/CFS from donating blood.

### Recommendations Prior to Surgery

For individuals with ME/CFS approaching surgery, discussion with the surgeon and anesthesiologist/anaesthetist about this illness is important. Issues such as depleted blood volume, orthostatic intolerance, pain control, and sensitivity to anesthetic medications should be addressed. Further recommendations for persons with ME/CFS who are anticipating surgery are given in Appendix E in the original guideline document.

## Clinical Algorithm(s)

None provided

## Scope

## Disease/Condition(s)

Chronic fatigue syndrome, also known as myalgic encephalomyelitis

## Guideline Category

Diagnosis

Management

Treatment

## Clinical Specialty

Family Practice

Internal Medicine

Neurology

Obstetrics and Gynecology

Pediatrics

Physical Medicine and Rehabilitation

Psychiatry

Psychology

## Intended Users

Advanced Practice Nurses

Physical Therapists

Physician Assistants

Physicians

Psychologists/Non-physician Behavioral Health Clinicians

## Guideline Objective(s)

To provide the information necessary to understand, diagnose, and manage the symptoms of chronic fatigue syndrome—also known as myalgic encephalomyelitis (ME/CFS)

## Target Population

Patient suspected of having or diagnosed with chronic fatigue syndrome—also known as myalgic encephalomyelitis (ME/CFS)

## Interventions and Practices Considered

Diagnosis

1. Medical and social history

2. Physical examination
3. Measuring severity and frequency of symptoms (pathological fatigue, post-exertional malaise, sleep problems, pain, two neurocognitive symptoms, and at least one symptom from two of the following categories: autonomic, neuroendocrine, immune)
4. Routine laboratory tests, electrocardiogram, chest x-ray
5. Differential diagnosis
6. Distinguishing myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) from depressive and anxiety disorders
7. Identifying and treating exclusionary and co-existing medical conditions

## Management/Treatment

1. Treating symptoms and guiding patient self-management
2. Management of sleep disorders (sleep hygiene and medications)
3. Management of pain (nonpharmacologic interventions and medications)
4. Management of fatigue and post-exertional malaise (pacing activities, activity logs, exercise and activity programs, medications for fatigue)
5. Management of cognitive problems
6. Management of depression, anxiety and distress (providing support, coping skills, engaging in pleasant experiences, medication)
7. Cognitive behavioral therapy
8. Management of related conditions (orthostatic intolerance and cardiovascular symptoms, gastrointestinal problems, urinary problems, allergies, multiple chemical sensitivity, infections and immunological factors)
9. Dietary management (e.g., supplements)
10. Alternative and complementary approaches
11. Regular follow-up and reassessment of symptoms
12. Special considerations for low-functioning patients
13. Management of pregnant women and women with gynecological problems
14. Management of children with ME/CFS
15. Avoiding all but essential immunizations, particularly with live vaccines
16. Discouraging or prohibiting individuals diagnosed with ME/CFS from donating blood
17. Preparing for surgery

## Major Outcomes Considered

- Symptom reduction
- Quality of life

## Methodology

### Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

### Description of Methods Used to Collect/Select the Evidence

Ovid/Medline was searched for articles from the time period of 1984 to May 2012 using the search term "chronic fatigue syndrome."

### Number of Source Documents

Not stated

### Methods Used to Assess the Quality and Strength of the Evidence

Not stated

## Rating Scheme for the Strength of the Evidence

Not applicable

## Methods Used to Analyze the Evidence

Review

## Description of the Methods Used to Analyze the Evidence

Not stated

## Methods Used to Formulate the Recommendations

Expert Consensus

## Description of Methods Used to Formulate the Recommendations

The text was developed by consensus of the primer committee. The authors have made considerable efforts to ensure that the information provided is accurate and up to date. Where published studies are lacking, the recommendations are based on the clinical expertise of the committee's experienced practitioners.

## Rating Scheme for the Strength of the Recommendations

Not applicable

## Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

## Method of Guideline Validation

Not stated

## Description of Method of Guideline Validation

Not applicable

## Evidence Supporting the Recommendations

### Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated for each recommendation.

Where published studies are lacking, the Writing Committee's recommendations are based on the clinical expertise of the Committee's experienced practitioners.

# Benefits/Harms of Implementing the Guideline Recommendations

## Potential Benefits

Accurate diagnosis and appropriate treatment and management of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)

## Potential Harms

- *Medications for sleep:* Patients may initially feel thick-headed in the morning, but this usually improves as benefits become apparent. The risk of side effects and drug combinations which can produce serotonin syndrome should be explained. In some patients, tolerance may develop with medications. See Table 5 in the original guideline document for specific potential side effects of medications for sleep.
- *Non-pharmacologic interventions for pain:* These interventions may be poorly tolerated, inaccessible, or prohibitively costly.
- *Medications for pain:* See Table 6 in the original guideline document for specific potential side effects of medications for pain.
- *Medications for fatigue:* Due to prescribing difficulties, cost, and limited effectiveness, medications for fatigue may need to be reserved for functional assistance at special, but potentially exhausting events in the patient's life (e.g., a wedding or a concert). See Table 7 in the original guideline document for specific potential side effects of medications for fatigue.
- *Medications for cognitive problems:* See Table 8 in the original guideline document for potential side effects of medications for cognitive problems.
- *Medications for depression:* Possible side effects of antidepressants, notably sedation and orthostatic hypotension, may worsen fatigue and autonomic lability in some patients. Drug choice is often based on side effects profile and the patient's response.
- *Herbs:* Patient use of herbal/natural remedies should be identified to reveal likely side effects and avoid potential conflicts with prescribed medications. Patients may not know that "natural" does not necessarily mean "better" or "safe." As with medication, small doses should be used initially with warnings about adverse reactions.

## Qualifying Statements

### Qualifying Statements

This primer was developed by consensus among members of the primer committee who have made considerable effort to ensure that the information is accurate and up to date with the caveat that the physiological basis of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) has not yet been established. Statements, opinions and study results published in this primer are those of the individual authors and the studies cited, and do not necessarily reflect the policy or position of the International Association for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (IACFS/ME). The IACFS/ME provides no warranty, express or implied, as to the accuracy or reliability of all the contents of this primer. The recommendations contained in any part of this primer do not indicate an exclusive course of treatment or course of action. Nothing contained in this primer should serve as a substitute for the medical judgment of a treating provider.

## Implementation of the Guideline

### Description of Implementation Strategy

An implementation strategy was not provided.

### Implementation Tools

Chart Documentation/Checklists/Forms

For information about availability, see the *Availability of Companion Documents and Patient Resources* fields below.

# Institute of Medicine (IOM) National Healthcare Quality Report Categories

## IOM Care Need

Living with Illness

## IOM Domain

Effectiveness

Patient-centeredness

## Identifying Information and Availability

### Bibliographic Source(s)

International Association for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (IACFS/ME). Chronic fatigue syndrome/myalgic encephalomyelitis. A primer for clinical practitioners. Chicago (IL): International Association for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (IACFS/ME); 2012. 41 p. [121 references]

### Adaptation

Not applicable: The guideline was not adapted from another source.

### Date Released

2012

### Guideline Developer(s)

International Association for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis - Nonprofit Organization

### Source(s) of Funding

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### Guideline Committee

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## Financial Disclosures/Conflicts of Interest

The International Association for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (IACFS/ME) received a \$10,000 donation from Hemispherx, the maker of Ampligen® (a possible treatment for ME/CFS), which supported this primer. Charles Lapp is a Hemispherx principal investigator in Ampligen® studies and has a small amount of stock in the company. Lucinda Bateman has been a principal investigator in Hemispherx Ampligen® studies for 10 years. All other authors declared no conflicts of interest.

## Guideline Status

This is the current release of the guideline.

## Guideline Availability

Electronic copies: Available in Portable Document Format (PDF) from the [International Association for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis \(IACFS/ME\) Web site](#) .

## Availability of Companion Documents

The following items are available in the [original guideline document](#) .

- Myalgia encephalomyelitis/chronic fatigue syndrome (ME/CFS) clinical diagnostic criteria worksheet
- 1994 international research case definition worksheet
- Pediatric case definition worksheet
- Functional capacity scale
- Activity log
- Recommendations prior to surgery

A variety of other resources, including a quick start guide to diagnosis and diagnosis questionnaires for adults and children, are available from the [International Association for Chronic Fatigue/Myalgic Encephalomyelitis \(IACFS/ME\) Web site](#) .

## Patient Resources

None available

## NGC Status

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